REMARKS/ARGUMENTS

Following entry of the present amendment, claims 1, 7-10, and 21-41 are pending and under consideration. The Examiner previously withdrew claims 2-5 and 11-20 from consideration as being drawn to nonelected inventions. Office Action at page 2, item no. 3. Applicants have canceled claims 2-6 and 11-20 without prejudice to or disclaimer of the subject matter recited therein. Applicants expressly reserve the right to pursue subject matter of those claims in one or more continuation and/or divisional applications at a future time. In the present amendment, Applicants have amended claims 1, 7, 8, and 10, and added new claims 21-41 as explained below. No new matter has been added by the amendments or new claims.

Applicants have amended claim 1 to specify

the method comprises:

obtaining an in-vivo patient sample from a patient suspected of having leukemia, pre-leukemia or aleukemic malignant blood disease;

contacting the patient sample with one or more anti-SCGF antibodies;

detecting and/or quantifying SCGF present in the patient sample in an immunological assay; thereby obtaining a patient sample SCGF value;

comparing the patient sample SCGF value to a SCGF cut-off value;

wherein the SCGF cut-off value is set based on one or more individuals that do not have leukemia, pre-leukemia, or aleukemic malignant blood disease; and

diagnosing leukemia, pre-leukemia or aleukemic malignant blood disease if the patient sample SCGF value is above the SCGF cut-off value.

Support for those amendments may be found throughout the specification, for example, at page 11, line 26, to page 12, line 15; at page 22, lines 9-10, and 12-14; at pages 22-23, last sentence bridging pages 22-23; at page 24, lines 4-7; at page 57, lines 2-8; at page 58, lines 6-14; and original claim 6. Claim 7 has been amended to depend from claim 1. The amendments to

claims 8 and 10 are merely grammatical changes to reflect typical claim language usage. No new matter has been added by those amendments.

Applicants have added new claims 21-41, all of which ultimately depend from claim 1. New claim 21 depends from claim 1 and further specifies

> the SCGF cut-off value is set by
>
> obtaining one or more in-vivo normal samples from one or more individuals that do not have leukemia, pre-leukemia, or aleukemic malignant blood disease;
>
> contacting the one or more normal samples with one or more anti-SCGF antibodies;
>
> detecting and/or quantifying SCGF present in the one or more normal samples in an immunological assay; thereby obtaining one or more normal sample SCGF values; and
>
> setting the SCGF cut-off value based on the one or more normal sample SCGF values.

Support for that claim is found in the specification, for example, at page 57, lines 2-13.

New claim 22 depends from claim 1 and further specifies "the in-vivo sample is selected from blood, urine, spinal fluid, and puncture fluid." New claim 23 depends from claim 22 and further specifies "the blood is selected from whole blood, plasma, and serum." Support for these claims is found in the specification, for example, at page 14, lines 2-6.

New claims 24-26 each depend from claim 1 and further specify the SCGF cut-off value is 18.2 ng/ml, 15.0 ng/ml, and 13.0 ng/ml, respectively. Support for these claims is found in the specification, for example, at page 13, lines 18-25.

New claims 27-29 depend from claim 10 and further specify the monoclonal antibody is KM2142 produced by hybridoma FERM BP-7922, KM2804 produced by hybridoma FERM BP-7923, and KM2945 produced by hybridoma FERM BP-7924, respectively. Support for these claims is found in the specification, for example, at page 21, lines 12-28.

New claims 30, 34, and 36 each depend from claim 1 and further specify leukemia, pre-leukemia, and aleukemic malignant blood disease, respectively. New claims 31-33 depend from claim 30 and further specify the leukemia is ALL, AML, and CML, respectively. New claim 35 depends from claim 34 and further specifies the pre-leukemia is MDS. New claims 37-41 ultimately depend from claim 36 and further specify the aleukemic malignant disease is lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloma, and multiple myeloma, respectively. Support for these claims is found in the specification, for example, at page 11, lines 7-25.

Accordingly, new claims 21-41 add no new matter.

I. Acknowledgment of Papers Submitted

Applicants acknowledge, with appreciation, the Office's acknowledgment of the papers submitted under 35 U.S.C. § 119(a)-(d), which have been placed of record in the file. Office Action at page 2, item no. 4.

II. Objection to Claim 6

The Office objected to claim 6 "as being dependent on non-elected claim 5." Office Action at page 2, item no. 5. Applicants have canceled claim 6 without prejudice to or disclaimer of the subject matter recited therein. Applicants reserve the right to pursue subject matter of claim 6 in one or more continuation and/or divisional applications at a future time. Accordingly, the objection is moot. Applicants respectfully request withdrawal of the objection to claim 6.

III. Rejection of Claims 1 and 6-10 Under 35 U.S.C. § 112, Second Paragraph

The Office rejected claims 1 and 6-10 under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention." Office Action at page 2, item no. 7. Specifically, the

Office alleged that claim 1 is "incomplete for omitting essential steps, such omission amounting to a gap between the steps." *Id.* at page 3, item no. 8. Applicants respectfully traverse the rejection.

Solely to expedite prosecution and without acquiescing to the Office's contentions, Applicants have amended claim 1. Claim 1 recites:

> A method for diagnosing leukemia, pre-leukemia or aleukemic malignant blood diseases wherein stem cell growth factor (SCGF) in an in-vivo sample is quantified, wherein the method comprises:
>
> obtaining an in-vivo patient sample from a patient suspected of having leukemia, pre-leukemia or aleukemic malignant blood disease;
>
> contacting the patient sample with one or more anti-SCGF antibodies;
>
> detecting and/or quantifying SCGF present in the patient sample in an immunological assay; thereby obtaining a patient sample SCGF value;
>
> comparing the patient sample SCGF value to a SCGF cut-off value;
>
> wherein the SCGF cut-off value is set based on one or more individuals that do not have leukemia, pre-leukemia, or aleukemic malignant blood disease; and
>
> diagnosing leukemia, pre-leukemia or aleukemic malignant blood disease if the patient sample SCGF value is above the SCGF cut-off value

As the Office will surely recognize, claim 1 includes at least "a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination," as suggested by the Office. *See* Office Action at page 3, item no. 8. Accordingly, Applicants respectfully assert that claim 1 is clear and definite, as are claims 7-10 which ultimately depend from claim 1. Claim 6 has been canceled without prejudice or disclaimer as discussed above and thus, the rejection is moot with respect to

claim 6. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 and 6-10 under § 112, second paragraph, as allegedly being indefinite.

IV. Rejection of Claims 1 and 6-10 Under 35 U.S.C. § 112, First Paragraph

The Office rejected claims 1 and 6-10 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Office Action at page 3, item no. 10. Specifically, the Office alleged that "[t]he specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation." *Id.* Applicants respectfully traverse the rejection.

The Office alleged that "the Specification provides no data that there is a correlation between the levels of serum SCGF and predictability of blood disease." *Id.* at page 4. The Office purported to support this contention, alleging that

> the specification disclosed that 'in general the distribution of the measured values of a disease group of the interested **partially overlaps those of the non-disease group**'. . . . Moreover, the specification disclosed that there were patient[s] that were diagnosed as being disease negative in spite of being a disease patients. . . . The specification further disclosed that no significant differences was observed between the values of SCGF for patients of aplastic anemia and health[y] individuals. . . .

Id. at pages 3-4 (emphasis in original).

Applicants respectfully disagree with the Office's allegations. First, regarding the Office's contentions concerning aplastic anemia, Applicants wish to clarify that the present claims recite "[a] method for diagnosing leukemia, pre-leukemia or aleukemic malignant blood disease." As set forth in the Specification, exemplary diseases of leukemia, pre-leukemia, and aleukemic malignant blood disease do not include aplastic anemia. *See* Specification at page 11, lines 7-25. Accordingly, the teachings in the specification concerning aplastic anemia, and thus, the Office's contentions regarding such teachings, are totally irrelevant to the subject matter of the present claims.

Second, Applicants assert that the specification contains ample teachings, including data, showing a correlation between the levels of SCGF in an in-vivo sample, such as serum, and the predictability of leukemia, pre-leukemia or aleukemic blood diseases, such that the claimed methods of diagnosis are fully enabled. The claimed methods specify that "the patient sample SCGF value" is compared to "a SCGF cut-off value," and that leukemia, pre-leukemia or aleukemic malignant blood disease is diagnosed "if the patient sample SCGF value is above the SCGF cut-off value."

The term "cut-off value" is defined at page 12, lines 5-15, of the Specification. In addition, the specification refers to a textbook that provides further information concerning cut-off values and methods of diagnosis using cut-off values. *Id.* at lines 13-15. The Specification indicates that "[a] group is diagnosed with a cut-off value." *Id.* at line 19.

Furthermore, the specification states that "those diagnosed as negative in spite of being disease positives" are "false negatives." *Id.* at lines 21-22. The Specification explains the difference between such "false negatives" and "true positives," "false positives," and "true negatives." *See, e.g., id.* at lines 19-29. The Specification further explains how such true positives, false negatives, false positives, and true negatives are affected by sensitivity and specificity, "indexes used for the purpose of evaluating clinical availability of cut-off values." *Id.* at lines 16-29. Furthermore, the Specification explains how "clinical availability of cut-off values" are evaluated. *See, e.g., id.* at page 12, line 16, to page 13, line 10. In addition, the specification provides exemplary methods for setting cut-off values, and then explains in detail how to set numerous exemplary SCGF cut-off values for diagnosing leukemia, pre-leukemia or aleukemic malignant blood diseases. *See, e.g., id.* at page 13, line 11, to page 14, line 1. Thus, the Specification provides ample guidance concerning the term "cut-off value."

Guidance concerning the "correlation between the levels of serum SCGF and predictability of blood disease" is provided, for example, in the Examples section of the Specification. For example, Example 7, at pages 56-59, discusses at length serum SCGF concentration in patients with leukemia, pre-leukemia, and aleukemic malignant blood diseases and compares those values to serum SCGF concentration in healthy individuals, i.e., individuals not having leukemia, preleukemia, or akeukemic malignant blood disease. The data in Table 4 at page 57 shows that 100% of patients suffering from acute lymphoid leukemia (ALL), 100% of patients suffering from chronic myeloid leukemia (CML), and 100% of patients suffering from myelodysplastic syndrome (MDS) were diagnosed as having those diseases when the SCGF cut-off value was set at 18.2 ng/ml. In addition, the data in Table 4 shows that 85.7% of patients with acute myeloid leukemia (AML) or non-Hodgkins lymphoma (NHL), and 66.7% of patients with multiple myeloma (MM) were diagnosed as having those diseases when the SCGF cut-off value was set at 18.2 ng/ml. *Id.* Thus, the data shows a very high correlation between the levels of SCGF in an in-vivo sample, such as human serum as in Example 7, and the predictability of leukemia, pre-leukemia or aleukemic blood diseases, which would be readily recognized by one skilled in the art. Furthermore, if a higher or lower level of sensitivity and specificity is desired, one skilled in the art would readily understand how to simply re-set the cut-off value. Based on the additional disclosure in the specification concerning different cut-off values having different levels of sensitivity and specificity as discussed in the paragraph above, such re-setting of the cut-off value, if desired, would not require undue experimentation.

Applicants also dispute the Office's allegation that "based on the data presented Fig. 7 one skill[ed] in the art would not recognize[ ] that there is any statistically significant differences between the levels of SCGF in the serum of healthy individuals and those with leukemia." Office Action at page 4. As explained in the Specification, "Fig. 7 shows SCGF concentrations

in the sera of patients suffering various blood diseases. The horizontal full lines show the medians of various blood disease groups and the horizontal dotted line shows the cut-off value calculated from the healthy individual group (18.2 ng/ml)." Specification at page 9, lines 23-27. Looking at Figure 7, one skilled in the art would easily discern that the median SCGF values for patients with ALL, AML, CML, MDS, NHL, and MM are all above the cut-off value calculated from the healthy individual group. Moreover, the Specification discusses p values of < 0.05 for each of the SCGF values for patients with ALL, AML, CML, MDS, NHL, and MM compared to the normal group and states that those p values are a "significant difference." *See, e.g., id.* at page 9, line 28 to page 10, line 2. Methods of calculating p values are well known to one skilled in the art, and a p value of < 0.05 is widely accepted by one skilled in the art as a standard of a statistically significant difference. Accordingly, one skilled in the art would readily recognize that the data in Figure 7 shows a statistically significant difference in the serum SCGF levels in patients with ALL, AML, CML, MDS, NHL, and MM compared to healthy (normal) individuals.

The Office also alleged that "[t]he specification does not provide sufficient teaching as to how it can be assessed that a patient has leukemia, pre-leukemia or aleukemic malignant blood disease by quantifying the levels of SCG[F]." Office Action at page 4. The Office acknowledged that "the specification describes the means of measuring the levels of SCGF in the serum of patient," but contended again that "there is no correlation on this record between the levels of said growth factor and a proposed method for diagnosing leukemia, pre-leukemia, or aleukemic malignant blood diseases in currently available form for humans or animals." *Id.* Applicants respectfully assert that the Specification provides ample guidance concerning such correlations as discussed at length above.

In addition, the Office cites *Ex Parte Maas*, 9 USPQ2d 1746, 1747-48 (BPAI 1987) for the proposition that "[i]t is not enough to rely on *in vivo* studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to efficacy in humans or animals." Applicants assert that the Office's reliance on *Ex Parte Maas* is misplaced for several reasons. First, the claims at issue in *Maas* were directed to methods of vaccinating humans or animals to achieve immune protection against pathogenic *E. coli*. *Id.* at 1747. The Board found that "the **utility** in question is sufficiently unusual to justify an examiner's requiring substantiating evidence. Substantiating evidence may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans." *Id.* (emphasis added). Thus, unlike the present claims, the claims in *Maas* were rejected for **lack of utility**, although an issue of an enabling disclosure was subsumed within the issue relating to patentable utility. *See id.* Here, the Office has not alleged that the present claims lack patentable utility, nor has the Office alleged that they present an unusual utility "requiring substantiating evidence." Therefore, the issues presented by *Maas* are inapplicable here. Second, as discussed at length above, the Specification provides ample teachings, including data, showing a clear correlation between the levels of SCGF in an in-vivo sample, such as human serum, and the predictability of leukemia, pre-leukemia or aleukemic malignant blood diseases. Thus, to the extent the Office believes "substantiating evidence" is relevant to the rejection, Applicants assert that such evidence is clearly and amply provided throughout the Specification, including, for example, in Example 7 at pages 56-59, in Table 4 at page 57, and in Figure 7. Therefore, *Ex Parte Maas* simply does not apply to the rejection of the present claims.

In summary, the discussion above clearly demonstrates that the Specification fully enables the scope of claims 1 and 7-10. Claim 6 has been canceled without prejudice or

disclaimer as discussed above, and thus, the rejection is moot with respect to that claim. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 and 6-10 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled.

As a final point, Applicants note the Office's statement "that the[re] is no recognition in the prior art that the levels of SCGF in serum of the patients can serve as an indicative of leukemia, pre-leukemia or aleukemic malignant blood disease." Office Action at page 4. Of course, the present claims encompass such subject matter. Thus, Applicants appreciate the Office's acknowledgment of the patentability of the present claims over the prior art.

CONCLUSION

Applicants respectfully request reconsideration of this application, withdrawal of all objections and rejections, and the timely allowance of the pending claims. In the event that the Examiner does not find the claims allowable, Applicants request that the Examiner contact the undersigned at (650) 849-6749 to set up an interview. Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Date: December 12, 2007

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